Clinical Evaluation of Hyaluronic Acid Combined with Tolmetin in the Treatment of Osteoarthritis of the Knee

Shaojin Wang, Peixue Ling, Yanli He, Tianmin Zhang

1 Introduction

The treatment of osteoarthritis (OA) of the knee is directed towards the relief of symptoms. Nonsteroidal anti-inflammatory drugs (NSAIDs) play an important role due to their dual analgesic and anti-inflammatory action. Side effects are the primary problems in many patients, leading to cessation of therapy. The local application of NSAIDs can avoid these effects by delivering low doses directly to the affected site.

High-molecular-weight sodium hyaluronate (HA) solution injected intra-articularly is proved to be effective in the treatment of OA of the knee by a great deal of clinical reports. In this paper, we report and evaluate the efficacy and safety of the formulation on volunteers with OA of the knee.

2 Materials & Methods

2.1 Patients

67 out-patients of either sex with idiopathic OA of the knee were enrolled in a six-week, double-blind trial of HA-tolmetin versus HA as control.

Inclusion criteria: age 18~70; OA of the knee verified by clinical examination, laboratory tests and radiographs according to Altman; for patients taking NSAIDs or glucocorticoids, the wash-out time should be no less than 2 weeks.

Exclusion criteria: accompanying OA of the hip, which could confuse assessment; patients with malfunction of liver and kidney.

2.2 Drug

HA-tolmetin Injection: 2ml contains 20mg of HA (mean molecular weight range $1.5 \times 10^6$~$2.0 \times 10^6$ Da) and 10mg of tolmetin sodium, provided by Shandong C.P. Freda Pharm. Co.

HA Injection: Sofast\textsuperscript{TM}, 2ml contains 20mg of HA with a mean molecular weight range $1.5 \times 10^6$~$2.0 \times 10^6$ Da, provided by Shandong C.P. Freda Pharm. Co.

2.3 Treatment

On entering the trial, patients were divided randomly to either the HA-tolmetin or HA group, and
underwent a series of pre-treatment assessments and necessary laboratory investigations. All injections were given intra-articularly once a week for consecutive 5 weeks. The injections of drugs and assessments were performed by different surgeons to eliminate any possible bias.

Corticosteroids, other NASIDs and analgesics were not permitted to be used in any form during the treatment period.

2.4 Evaluation of efficacy

The index assessed and scored according to Lequesne [2]: (1) Activities of daily living (ADL) including 4 different activities, each being scored on 4-point scale (0= no difficulty to 3= activity impossible). The activities were: getting up from sitting, climbing up and down stairs, squatting or bending on the knee, walking on uneven ground; (2) The grading of the severity of pain on movement, pain at rest and pain on press were assessed using 10 cm visual analogue scales (VAS) [3].

All patients were assigned to one of the five severity grades according their scores before and after treatment respectively. Grade I: \( \geq 30 \); Grade II: 20~29; Grade III: 11~19; Grade IV: 5~10; Grade V: 0~4.

The efficacy was divided into four grades. Excellent: scores for all indices were down to 0, or the severity grade decreased no less than 4 grades at the end of the treatment. Good: the severity grade decreased no less than 3 grades at the end of the treatment. Fair: the severity grade decreased by 1~2 grades at the end of the treatment. Poor: the decrease in severity grade did not surpassed original grade at the end of the treatment.

2.5 Evaluation of safety

Before and after the treatment, urine and venous blood samples of each patient were tested for routine urinoscopy, hematological and blood biochemical screen investigation, and all suspected adverse reactions were recorded.

2.6 Statistical analysis

Wilcoxon's Signed Rank Tests and T-tests were used to analyze the significance of the difference between the two groups before and after treatment. Two-tailed statistical tests were used and \( P=0.05 \) was taken as the threshold above which differences or changes are considered as
3 Results & Discussion

The detailed information of patients in the two groups was listed in Table 1. All patients completed the trial. There were no significant differences ($P \geq 0.05$) in sex, age and the distribution of severity grades between the two groups before treatment.

### Table 1. The information of the patients in the two treatment groups before treatment

<table>
<thead>
<tr>
<th>Groups</th>
<th>No.</th>
<th>Sex</th>
<th>Age (mean)</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Male</td>
<td>14-65 (53.1)</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Female</td>
<td>21</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>14</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>HA-tolmetin</td>
<td>34</td>
<td>12</td>
<td>21</td>
<td>6</td>
</tr>
<tr>
<td>HA</td>
<td>33</td>
<td>11</td>
<td>22</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>22</td>
<td>62 (50.5)</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

3.1 ADL

There were progressive reductions in mean scores during the 5 week treatment in both groups (Table 2, Figure 1). After the treatment, there was significant difference between the two groups ($P<0.01$).

### Table 2. The changes in the mean scores of ADL and pain during the treatment period (mean ±SD)

<table>
<thead>
<tr>
<th>Group</th>
<th>ADL Pre-treatment</th>
<th>Post-treatment</th>
<th>Pain Pre-treatment</th>
<th>Post-treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>HA-tolmetin</td>
<td>7.91 ± 1.96*</td>
<td>1.68 ± 1.80**</td>
<td>16.90 ± 4.08*</td>
<td>1.18 ± 2.34**</td>
</tr>
<tr>
<td>HA</td>
<td>7.30 ± 1.76</td>
<td>2.82 ± 2.21</td>
<td>16.27 ± 4.08</td>
<td>4.00 ± 3.00</td>
</tr>
</tbody>
</table>

*: $P \geq 0.05$, **: $P<0.01$.

3.2 Pain

Progressive reductions in mean pain scores were also found in both treatment groups during the 5 week treatment (Table 2 and Figure 2).
During the treatment period, there were progressive reductions in both groups, the mean score reduction was greater in HA-tolmetin group than in HA group, and the difference was significant ($P<0.01$).

![Graph showing changes in mean scores of ADL](image1)

**Figure 1.** The changes in the mean scores of ADL during the treatment period

![Graph showing progressive reductions in mean scores of pain](image2)

**Figure 2.** Progressive reductions in the mean scores of pain during the treatment period

### 3.3 Efficacy evaluation
The distribution of severity of patients and the efficacy evaluated by doctors and patients at the end of the treatment was listed in the table 3.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Severity grade</th>
<th>Efficacy by doctors</th>
<th>Efficacy by patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I</td>
<td>II</td>
<td>III</td>
</tr>
<tr>
<td>HA-tolmetin</td>
<td>0</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>HA</td>
<td>0</td>
<td>0</td>
<td>6</td>
</tr>
</tbody>
</table>

*: $P<0.01$, **: $P<0.05$.

3.4 Side effect

Possibly drug-related events were reported by 3 patients in HA group after the third injection, but none in HA-tolmetin group. The joints of all the 3 patients swelled with aggravated pain several hours after injection, and the signs disappeared within 3 days since it occurred without treatment.

All of the laboratory screening investigations were not changed significantly.

Tolmetin effectively suppresses inflammation and is used widely in the treatment of OA. The oral administration dose is 900~1200mg per day. Many patients can't tolerate its side effects, which limit its use in chronic disease such as OA. In this paper, the intra-articular injection dose of tolmetin is 10 mg once a week, and no adverse effects were observed. The results suggest that the formulation may represent a valuable approach to the patients with OA of the knee with more efficacy and safety.

Reference


[原文发表于: Hyaluronan(Vol 2), Cambridge, 2002. 397~400]